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(54) Title: SUBSTITUTED PYRROLE DERIVATIVES AS CELL ADHESION INHIBITORS

(57) Abstract

Substituted pyrrole derivatives of Formula (I) are antagonists of VLA-4 and/or $\alpha_4\beta_7$, and as such are useful in the inhibition or prevention of cell adhesion and cell-adhesion mediated pathologies. These compounds may be formulated into pharmaceutical compositions and are suitable for use in the treatment of asthma, allergies, inflammation, multiple sclerosis, and other inflammatory and autoimmune disorders.

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TITLE OF THE INVENTION
SUBSTITUTED PYRROLE DERIVATIVES AS CELL ADHESION
INHIBITORS

5 BACKGROUND OF THE INVENTION

The present invention relates to novel substituted pyrrole derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and 10 methods of treatment using such compounds.

Many physiological processes require that cells come into close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions 15 are mediated through several families of cell adhesion molecules (CAMs) including the selectins, integrins, cadherins and immunoglobulins. CAMs play an essential role in both normal and pathophysiological processes. Therefore, the targetting of specific and relevant CAMs in certain disease conditions without interfering with 20 normal cellular functions is essential for an effective and safe therapeutic agent that inhibits cell-cell and cell-matrix interactions.

The integrin superfamily is made up of structurally and functionally related glycoproteins consisting of α and β heterodimeric, transmembrane receptor molecules found in various combinations on 25 nearly every mammalian cell type. (for reviews see: E. C. Butcher, Cell, 67, 1033 (1991); T. A. Springer, Cell, 76, 301 (1994); D. Cox et al., "The Pharmacology of the Integrins." Medicinal Research Rev. 14, 195 (1994) and V. W. Engleman et al., "Cell Adhesion Integrins as Pharmaceutical Targets." in Ann. Repts. in Medicinal Chemistry, Vol. 31, J. A. Bristol, 30 Ed.; Acad. Press, NY, 1996, p. 191).

VLA-4 ("very late antigen-4"; CD49d/CD29; or $\alpha 4\beta 1$) is an integrin expressed on all leukocytes, except platelets and mature neutrophils, including dendritic cells and macrophage-like cells and is a key mediator of the cell-cell and cell-matrix interactions of these cell types 35 (see M. E. Hemler, "VLA Proteins in the Integrin Family: Structures, Functions, and Their Role on Leukocytes." Ann. Rev. Immunol. 8, 365

(1990)). The ligands for VLA-4 include vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 domain of fibronectin (FN). VCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells at sites of inflammation. (See R. Lobb et al. "Vascular Cell Adhesion Molecule 1." in *Cellular and Molecular Mechanisms of Inflammation*, C. G. Cochrane and M. A. Gimbrone, Eds.; Acad. Press, San Diego, 1993, p. 151.) VCAM-1 is produced by vascular endothelial cells in response to pro-inflammatory cytokines (See A. J. H. Gearing and W. Newman, "Circulating adhesion molecules in disease.", *Immunol. Today*, 14, 506 (1993). The CS-1 domain is a 25 amino acid sequence that arises by alternative splicing within a region of fibronectin. (For a review, see R. O. Hynes "Fibronectins.", Springer-Velag, NY, 1990.) A role for VLA-4/CS-1 interactions in inflammatory conditions has been proposed (see M. J. Elices, "The integrin $\alpha_4\beta_1$ (VLA-4) as a therapeutic target" in *Cell Adhesion and Human Disease*, Ciba Found. Symp., John Wiley & Sons, NY, 1995, p. 79).

$\alpha_4\beta_7$ (also referred to as LPAM-1 and $\alpha_4\beta_p$) is an integrin expressed on leukocytes and is a key mediator of leukocyte trafficking and homing in the gastrointestinal tract (see C. M. Parker et al., *Proc. Natl. Acad. Sci. USA*, 89, 1924 (1992)). The ligands for $\alpha_4\beta_7$ include mucosal addressing cell adhesion molecule-1 (MadCAM-1) and, upon activation of $\alpha_4\beta_7$, VCAM-1 and fibronectin (Fn). MadCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells of gut-associated mucosal tissues of the small and large intestine ("Peyer's Patches") and lactating mammary glands. (See M. J. Briskin et al., *Nature*, 363, 461 (1993); A. Hamann et al., *J. Immunol.*, 152, 3282 (1994)). MadCAM-1 can be induced *in vitro* by proinflammatory stimuli (See E. E. Sikorski et al. *J. Immunol.*, 151, 5239 (1993)). MadCAM-1 is selectively expressed at sites of lymphocyte extravasation and specifically binds to the integrin, $\alpha_4\beta_7$.

Neutralizing anti- α_4 antibodies or blocking peptides that inhibit the interaction between VLA-4 and/or $\alpha_4\beta_7$ and their ligands have proven efficacious both prophylactically and therapeutically in several animal models of disease, including i) experimental allergic encephalomyelitis, a model of neuronal demyelination resembling multiple sclerosis (for example, see T. Yednock et al., "Prevention of

experimental autoimmune encephalomyelitis by antibodies against $\alpha_4\beta_1$ integrin." Nature, 356, 63 (1993) and E. Keszthelyi et al., "Evidence for a prolonged role of α_4 integrin throughout active experimental allergic encephalomyelitis." Neurology, 47, 1053 (1996)); ii) bronchial 5 hyperresponsiveness in sheep and guinea pigs as models for the various phases of asthma (for example, see W. M. Abraham et al., " α_4 -Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest., 93, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte 10 recruitment and bronchial hyperresponsiveness in the guinea-pig." Eur. J. Pharmacol., 282, 243 (1995)); iii) adjuvant-induced arthritis in rats as a model of inflammatory arthritis (see C. Barbadillo et al., "Anti-VLA-4 mAb prevents adjuvant arthritis in Lewis rats." Arthr. Rheuma. (Suppl.), 36 95 (1993) and D. Seiffge, "Protective effects of monoclonal 15 antibody to VLA-4 on leukocyte adhesion and course of disease in adjuvant arthritis in rats." J. Rheumatol., 23, 12 (1996)); iv) adoptive autoimmunity diabetes in the NOD mouse (see J. L. Baron et al., "The pathogenesis of adoptive murine autoimmunity diabetes requires an interaction between α_4 -integrins and vascular cell adhesion molecule- 20 1.", J. Clin. Invest., 93, 1700 (1994), A. Jakubowski et al., "Vascular cell adhesion molecule-Ig fusion protein selectively targets activated α_4 -integrin receptors in vivo: Inhibition of autoimmunity diabetes in an adoptive transfer model in nonobese diabetic mice." J. Immunol., 155, 938 (1995), and X. D. Yang et al., "Involvement of beta 7 integrin and 25 mucosal addressin cell adhesion molecule-1 (MadCAM-1) in the development of diabetes in nonobese diabetic mice", Diabetes, 46, 1542 (1997)); v) cardiac allograft survival in mice as a model of organ transplantation (see M. Isobe et al., "Effect of anti-VCAM-1 and anti-VLA-4 monoclonal antibodies on cardiac allograft survival and response 30 to soluble antigens in mice.", Transplant. Proc., 26, 867 (1994) and S. Molossi et al., "Blockade of very late antigen-4 integrin binding to fibronectin with connecting segment-1 peptide reduces accelerated coronary arteropathy in rabbit cardiac allografts." J. Clin. Invest., 95, 2601 (1995)); vi) spontaneous chronic colitis in cotton-top tamarins which 35 resembles human ulcerative colitis, a form of inflammatory bowel disease (see D. K. Podolsky et al., "Attenuation of colitis in the Cotton-top

tamarin by anti- α_4 integrin monoclonal antibody.", J. Clin. Invest., **92**, 372 (1993)); vii) contact hypersensitivity models as a model for skin allergic reactions (see T. A. Ferguson and T. S. Kupper, "Antigen-independent processes in antigen-specific immunity.", J. Immunol., **150**, 1172 (1993) and P. L. Chisholm et al., "Monoclonal antibodies to the integrin α -4 subunit inhibit the murine contact hypersensitivity response." Eur. J. Immunol., **23**, 682 (1993)); viii) acute neurotoxic nephritis (see M. S. Mulligan et al., "Requirements for leukocyte adhesion molecules in nephrotoxic nephritis.", J. Clin. Invest., **91**, 577 (1993)); ix) tumor metastasis (for examples, see M. Edward, "Integrins and other adhesion molecules involved in melanocytic tumor progression.", Curr. Opin. Oncol., **7**, 185 (1995)); x) experimental autoimmune thyroiditis (see R. W. McMurray et al., "The role of α_4 integrin and intercellular adhesion molecule-1 (ICAM-1) in murine experimental autoimmune thyroiditis." Autoimmunity, **23**, 9 (1996); and xi) ischemic tissue damage following arterial occlusion in rats (see F. Squadrato et al., "Leukocyte integrin very late antigen-4/vascular cell adhesion molecule-1 adhesion pathway in splanchnic artery occlusion shock." Eur. J. Pharmacol., **318**, 153 (1996); xii) inhibition of TH2 T-cell cytokine production including IL-4 and IL-5 by VLA-4 antibodies which would attenuate allergic responses (J.Clinical Investigation **100**, 3083 (1997). The primary mechanism of action of such antibodies appears to be the inhibition of lymphocyte and monocyte interactions with CAMs associated with components of the extracellular matrix, thereby limiting leukocyte migration to extravascular sites of injury or inflammation and/or limiting the priming and/or activation of leukocytes.

There is additional evidence supporting a possible role for VLA-4 interactions in other diseases, including rheumatoid arthritis; various melanomas, carcinomas, and sarcomas; inflammatory lung disorders; acute respiratory distress syndrome (ARDS); atherosclerotic plaque formation; restenosis; uveitis and circulatory shock (for examples, see A. A. Postigo et al., "The $\alpha_4\beta_1$ /VCAM-1 adhesion pathway in physiology and disease.", Res. Immunol., **144**, 723 (1994) and J.-X. Gao and A. C. Issekutz, "Expression of VCAM-1 and VLA-4 dependent T-lymphocyte adhesion to dermal fibroblasts stimulated with proinflammatory cytokines." Immunol. **89**, 375 (1996)).

At present, there is a humanized monoclonal antibody (Antegren® Athena Neurosciences/Elan) against VLA-4 in clinical development for the treatment of "flares" associated with multiple sclerosis and a humanized monoclonal antibody (ACT-1®/LDP-02 5 LeukoSite) against $\alpha 4\beta 7$ in clinical development for the treatment of inflammatory bowel disease. Several peptidyl antagonists of VLA-4 have been described (D. Y. Jackson et al., "Potent $\alpha 4\beta 1$ peptide antagonists as potential anti-inflammatory agents", *J. Med. Chem.*, **40**, 3359 (1997); H. N. Shroff et al., "Small peptide inhibitors of $\alpha 4\beta 7$ mediated MadCAM-1 10 adhesion to lymphocytes", *Bioorg. Med. Chem. Lett.*, **6**, 2495 (1996); US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973). There is one report of nonpeptidyl inhibitors of the ligands for $\alpha 4$ -integrins (WO96/31206). There still remains a need for low molecular weight, specific inhibitors 15 of VLA-4- and $\alpha 4\beta 7$ -dependent cell adhesion that have improved pharmacokinetic and pharmacodynamic properties such as oral bioavailability and significant duration of action. Such compounds would prove to be useful for the treatment, prevention or suppression of various pathologies mediated by VLA-4 and $\alpha 4\beta 7$ binding and cell 20 adhesion and activation.

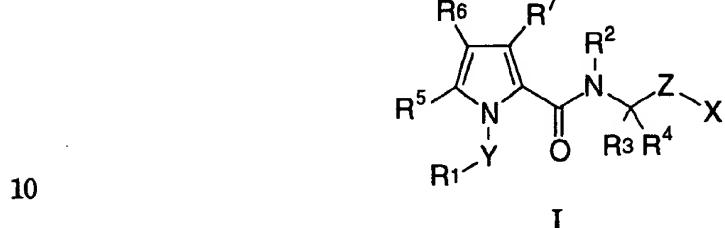
SUMMARY OF THE INVENTION

The compounds of the present invention are antagonists of the VLA-4 integrin ("very late antigen-4"; CD49d/CD29; or $\alpha 4\beta 1$) and/or 25 the $\alpha 4\beta 7$ integrin (LPAM-1 and $\alpha 4\beta p$), thereby blocking the binding of VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin and/or $\alpha 4\beta 7$ to its various ligands, such as MadCAM-1, VCAM-1 and fibronectin. Thus, these antagonists are useful in inhibiting cell 30 adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment, prevention and suppression of diseases mediated by VLA-4 and/or $\alpha 4\beta 7$ binding and cell adhesion and activation, such as multiple sclerosis, 35 asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory

bowel disease including ulcerative colitis and Crohn's disease, certain types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, and atherosclerosis.

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel compounds of
Formula I



or a pharmaceutically acceptable salt thereof wherein:

X is	1) $-\text{C}(\text{O})\text{OR}^{\text{d}}$,
15	2) $-\text{P}(\text{O})(\text{OR}^{\text{d}})(\text{OR}^{\text{e}})$
	3) $-\text{P}(\text{O})(\text{R}^{\text{d}})(\text{OR}^{\text{e}})$
	4) $-\text{S}(\text{O})_m\text{OR}^{\text{d}}$,
	5) $-\text{C}(\text{O})\text{NR}^{\text{d}}\text{R}^{\text{h}}$, or
	6) -5-tetrazolyl;
20 Y is	1) $-\text{C}(\text{O})-$,
	2) $-\text{O}-\text{C}(\text{O})-$,
	3) $-\text{NR}^{\text{e}}-\text{C}(\text{O})-$,
	4) $-\text{S}(\text{O})_2-$,
	5) $-\text{P}(\text{O})(\text{OR}^{\text{4}})$ or
25	6) $\text{C}(\text{O})\text{C}(\text{O})$;
Z is	1) a bond, or
	2) $-\text{C}(\text{R}^{\text{8}})(\text{R}^{\text{9}})-$;
R ¹ is	1) C ₁₋₁₀ alkyl,
	2) C ₂₋₁₀ alkenyl,
30	3) C ₂₋₁₀ alkynyl,
	4) Cy,
	5) Cy-C ₁₋₁₀ alkyl,

- 6) Cy-C₂-10alkenyl,
- 7) Cy-C₂-10alkynyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

5 R² is

- 1) hydrogen,
- 2) C₁-10 alkyl,
- 3) Cy,
- 4) Cy-C₁-10 alkyl,

10 wherein alkyl is optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

R³ is

- 1) hydrogen,
- 2) C₁-10alkyl,
- 3) C₂-10alkenyl,
- 4) C₂-10alkynyl,
- 5) Cy-(Cy)_p,
- 6) Cy-(Cy)_p-C₁-10alkyl,
- 7) Cy-(Cy)_p-C₂-10alkenyl,
- 8) Cy-(Cy)_p-C₂-10alkynyl,

15 alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

R⁴ is

- 1) hydrogen,
- 2) C₁-10alkyl,
- 3) C₂-10alkenyl,
- 4) C₂-10alkynyl,
- 5) Cy,
- 6) Cy-C₁-10alkyl,

20 30 wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b;

R⁵, R⁶, and R⁷ are each independently

- 1) hydrogen, or
- 2) a group selected from R^b; or

R⁵ and R⁶ or R⁶ and R⁷ and the two adjacent carbon atoms to which they are attached, together form a 5-7 membered saturated or unsaturated monocyclic ring containing zero to two heteroatoms selected from N, O or S;

5 R⁸ is 1) hydrogen,
2) a group selected from R^a, or
3) a group selected from R¹;

R⁹ is 1) hydrogen,
2) C₁₋₁₀alkyl,
10 3) C₂₋₁₀alkenyl,
4) C₂₋₁₀alkynyl,
5) Cy,
6) Cy-C₁₋₁₀alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to 15 four substituents selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b.

R^a is 1) -CF₃;
2) -ORD,
3) -NO₂,
20 4) halogen
5) -S(O)_mR^d,
6) -SR^d,
7) -S(O)₂ORD,
8) -S(O)_mNR^dRE,
25 9) -NR^dRE,
10) -O(CR^fRG)_nNR^dRE,
11) -C(O)R^d,
12) -CO₂R^d,
13) -CO₂(CR^fRG)_nCONR^dRE,
30 14) -OC(O)R^d,
15) -CN,
16) -C(O)NR^dRE,
17) -NR^dC(O)RE,
18) -OC(O)NR^dRE,
35 19) -NR^dC(O)ORE, or
20) -NR^dC(O)NR^dRE;

21) $\text{-CR}^d(\text{N-OR}^e)$, or

22) Cy optionally substituted with a group independently selected from R^c ;

5 R^b is 1) a group selected from R^a ,

2) C_{1-10} alkyl,

3) C_{2-10} alkenyl,

4) C_{2-10} alkynyl, or

5) Cy- C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, and Cy are optionally substituted with a

10 group independently selected from R^c ;

substituted with a group independently selected from R^c ;

15 R^c is 1) halogen,

2) amino,

3) carboxy,

4) C_{1-4} alkyl,

5) C_{1-4} alkoxy,

6) aryl,

7) aryl C_{1-4} alkyl, or

8) aryloxy;

20 R^d and R^e are independently selected from the group consisting of

1) hydrogen,

2) C_{1-10} alkyl,

3) C_{2-10} alkenyl,

4) C_{2-10} alkynyl,

25 5) Cy, and

6) Cy C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl and Cy is optionally substituted with one to four substituents independently selected from R^c ; or

30 R^d and R^e together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen; R^f and R^g are independently selected from hydrogen, C_{1-10} alkyl, Cy and Cy C_{1-10} alkyl; or

35 R^f and R^g together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^h is

- 1) hydrogen,
- 2) C₁₋₁₀alkyl,
- 3) C₂₋₁₀alkenyl,
- 4) C₂₋₁₀alkynyl,
- 5) cyano,
- 6) aryl,
- 7) aryl C₁₋₁₀alkyl,
- 8) heteroaryl,
- 9) heteroaryl C₁₋₁₀alkyl, or
- 10) -SO₂Rⁱ;

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from R^b;

Rⁱ

- 1) C₁₋₁₀alkyl,
- 2) C₂₋₁₀alkenyl,
- 3) C₂₋₁₀alkynyl, or
- 4) aryl;

wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^c;

Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

m is an integer from 1 to 2;

n is an integer from 1 to 10; and

p is 0 or 1.

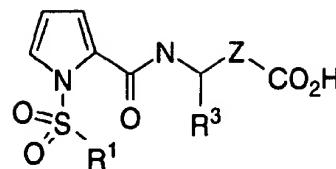
In one subset of compounds of formula I R¹ is Cy or Cy-C₁₋₁₀alkyl where Cy and alkyl are optionally substituted as provided above. For the purpose of R¹, Cy is preferably aryl optionally substituted with one or two groups selected from R^b.

In another subset of compounds of formula I Y is -C(O)- or

SO₂.

In another subset of compounds of formula I X is -C(O)OR^d.

A preferred embodiment of compound of formula I are compounds of formula Ia:



Ia

wherein

R1 is aryl optionally substituted with one or two groups

5 independently selected from R^b;

R3 is 1) C₁-10alkyl,

2) Cy-(Cy)_p, or

3) Cy-(Cy)_p-C₁-10alkyl,

wherein alkyl is optionally substituted with one to four substituents

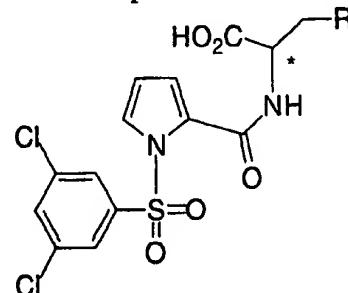
10 independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

Z is 1) a bond, or

2) -CH₂-; and

the other variables are as provided under formula I.

15 Representative compounds of formula I are as follows:



<u>Ex. No.</u>	<u>R</u>
1	phenyl
2	benzyl
3	propyl
4	4-(t-butoxyphenyl)
5	4-(benzyloxy)phenyl
6	4-(2-methoxyphenyl)phenyl
7	4-(3-methoxyphenyl)phenyl
8	4-(2-cyanophenyl)phenyl
9	4-(3-cyanophenyl)phenyl
10	4-(2-propyloxyphenyl)phenyl
11	4-(2-tetrazolylphenyl)phenyl
12	4-(2-methylthiophenyl)phenyl

13	4-(2-methylsulfonylphenyl)phenyl
14	4-hydroxyphenyl

* stereoconfiguration is that of an L-amino acid

5 "Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

10 "Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-but enyl, and the like.

15 "Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

20 "Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each of which having from 3 to 10 carbon atoms. The term also includes monocyclic ring fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the like.

25 "Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. The term also includes aryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of aryl include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, and the like.

30 "Heteroaryl" means a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl,

benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

"Heterocyclyl" means mono- or bicyclic saturated rings containing at least one heteroatom selected from N, S and O, each of said 5 ring having from 3 to 10 atoms. The term also includes monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of "heterocyclyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolinyl, 10 tetrahydroisoquinolinyl, dihydroindolyl, and the like.

"Halogen" includes fluorine, chlorine, bromine and iodine.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric 15 centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic 20 double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with 25 different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl 30 acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general 35 Formula I or Ia may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids.

5 Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganese, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic

10 non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-

15 dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine,

20 tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

35 Utilities

The ability of the compounds of Formula I to antagonize the actions of VLA-4 and/or $\alpha 4\beta 7$ integrin makes them useful for preventing or reversing the symptoms, disorders or diseases induced by the binding of VLA-4 and or $\alpha 4\beta 7$ to their various respective ligands. Thus, these antagonists will inhibit cell adhesion processes including cell activation, migration, proliferation and differentiation. Accordingly, another aspect of the present invention provides a method for the treatment (including prevention, alleviation, amelioration or suppression) of diseases or disorders or symptoms mediated by VLA-4 and/or $\alpha 4\beta 7$ binding and cell adhesion and activation, which comprises administering to a mammal an effective amount of a compound of Formula I. Such diseases, disorders, conditions or symptoms are for example (1) multiple sclerosis, (2) asthma, (3) allergic rhinitis, (4) allergic conjunctivitis, (5) inflammatory lung diseases, (6) rheumatoid arthritis, (7) septic arthritis, (8) type I diabetes, (9) organ transplantation rejection, (10) restenosis, (11) autologous bone marrow transplantation, (12) inflammatory sequelae of viral infections, (13) myocarditis, (14) inflammatory bowel disease including ulcerative colitis and Crohn's disease, (15) certain types of toxic and immune-based nephritis, (16) contact dermal hypersensitivity, (17) psoriasis, (18) tumor metastasis, (19) hepatitis, and (20) atherosclerosis.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound

of Formula I per kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

5 In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more 10 preferably from about 10 mg to about 100 mg) of a compound of Formula I per kg of body weight per day.

15 For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from 20 combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a 25 compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

30 Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, 35 parenteral, ocular, pulmonary, nasal, and the like may be employed.

Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

5 The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

10 The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions 15 being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

20 For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an 25 insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

30 In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., 35 oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical

media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, 5 microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent 10 the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the 15 compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention 20 suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier 25 which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or 30 molding, optionally with one or more accessory ingredients.

Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by 35 molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains

from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

5

	<u>Injectable Suspension (I.M.)</u>	<u>mg/mL</u>
	Compound of Formula I	10
	Methylcellulose	5.0
	Tween 80	0.5
10	Benzyl alcohol	9.0
	Benzalkonium chloride	1.0
	Water for injection to a total volume of 1 mL	

	<u>Tablet</u>	<u>mg/tablet</u>
15	Compound of Formula I	25
	Microcrystalline Cellulose	415
	Povidone	14.0
	Pregelatinized Starch	3.5
	Magnesium Stearate	2.5
20		500

	<u>Capsule</u>	<u>mg/capsule</u>
	Compound of Formula I	25
	Lactose Powder	573.5
25	Magnesium Stearate	1.5
		600

	<u>Aerosol</u>	<u>Per canister</u>
	Compound of Formula I	24 mg
30	Lecithin, NF Liquid Concentrate	1.2 mg
	Trichlorofluoromethane, NF	4.025 g
	Dichlorodifluoromethane, NF	12.15 g

Combination Therapy

35 Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or

amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of

5 Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a

10 compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(a) other VLA-4 antagonists such as those described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, 15 WO96/01644, WO96/06108, WO95/15973, WO96/31206 and WO98/42656; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and 20 other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as brompheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleannamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, 25 pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, 30 leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, 35 flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and

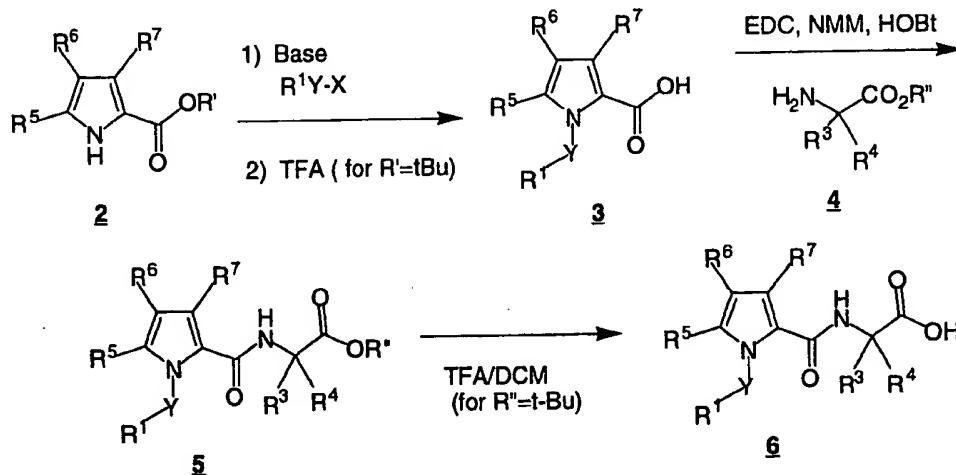
tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpina, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, 5 meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, 10 phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) antagonists of the chemokine receptors, especially CCR-1, CCR-2, and CCR-3; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, 15 atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone, 20 pioglitazone, englitazone, MCC-555, BRL49653 and the like); (l) preparations of interferon beta (interferon beta-1a, interferon beta-1b); (m) anticholinergic agents such as muscarinic antagonists (ipratropium bromide); (n) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. 25

The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is 30 combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective 35 dose of each active ingredient should be used.

The compounds of Formula I may be prepared by several general synthetic methods as described in for example, *Principles of Peptide Synthesis*, 2nd Ed., M. Bodanszky, Springer Verlag, Berlin Heidelberg, 1993. The compound of the present invention can be 5 prepared by procedures illustrated in the accompanying schemes. In general, these compounds are constructed in such a way that the pyrrole nitrogen is elaborated before modifications are made to the pyrrole 2-carbonyl position.

Although the reaction schemes described below are 10 reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of Formula I may render the molecule incompatible with a particular synthetic sequence. In such a case an alternative route, an altered order of steps, or a strategy of protection and deprotection may be 15 employed. In all cases the particular reaction conditions (including reagents, solvent, temperature, and time) should be chosen so that they are consistent with the nature of the functionalities present in the molecule.

Scheme 1

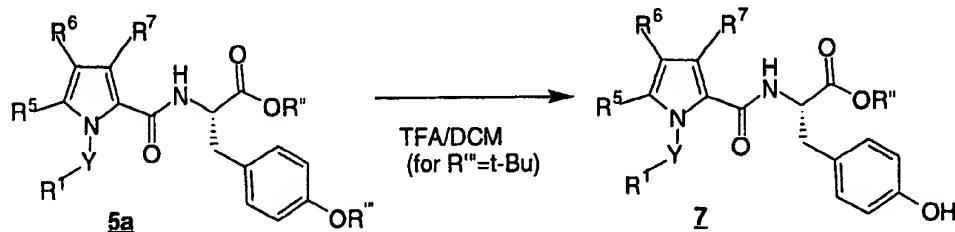


20 As shown in Scheme 1, a suitably substituted t-butyl pyrrole-2-carboxylate or equivalent (2, $\text{CO}_2\text{R}'$ = t-butyl ester or another ester which does not require base to hydrolyze) is acylated or sulfonylated

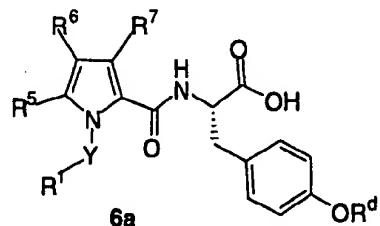
under phase transfer conditions based on an established method (see for example, Illi, V.O., *Synthesis*, 1979, 136; Anderson, H.J. et al., *Can. J. Chem.*, **63**, 1985, 896; Yajima, H. et al., *Chem. Pharm. Bull.*, **32**, 1984, 2660). The ester moiety is then hydrolyzed under appropriate non-basic 5 conditions to provide **3**. Compound **3** is then coupled with an appropriately elaborated amino acid ester **4** under suitable conditions to provide **5** which upon hydrolysis yields the target compound **6**.

Scheme 2 addresses further elaborations at R^3 and/or R^4 of compound **6**. The example shown is that for derivatizations on H-L-10 (OtBu)Tyr-(OR'') as **4**. Starting with **5a**, the free phenol is restored under standard conditions to provide the key intermediate **7**. This compound can be further elaborated for example via alkylation or acylation to grant entry into a variety of functional groups. When the desired R^d has been obtained, the ester is hydrolyzed to the acid to provide the desired targets 15 **6a**.

Scheme 2



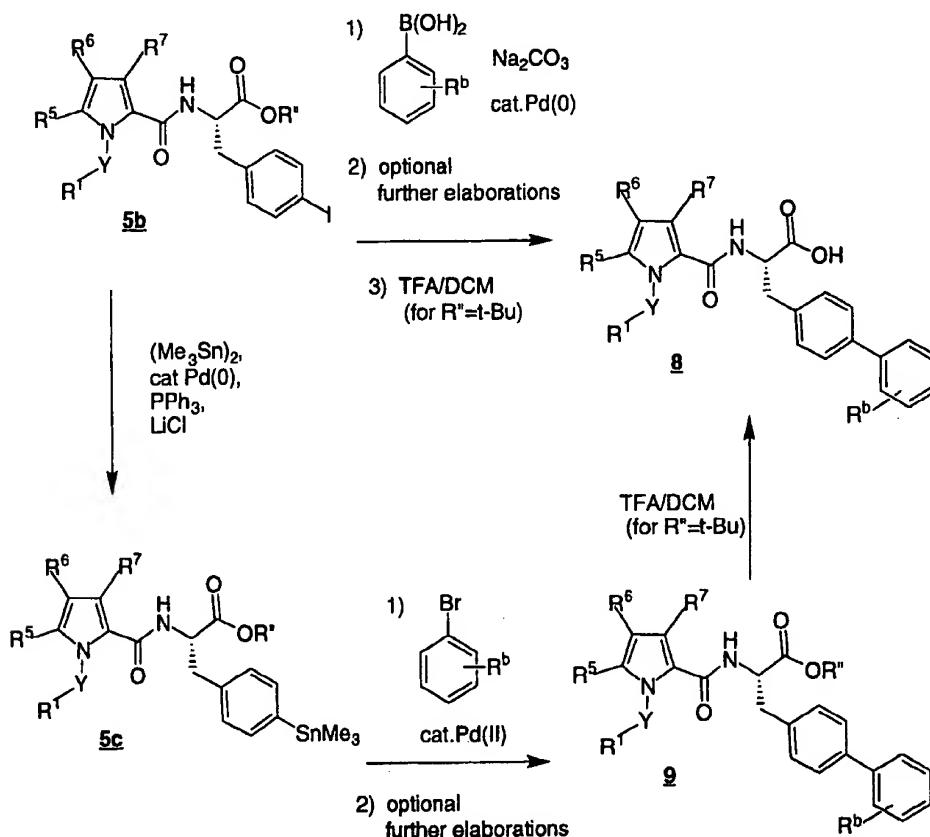
1) Base, RX (or ROH, PPh₃, DEAD), or base, RCOCl and/or further elaborations



Scheme 3 shows a route to elaborate R^3 and/or R^4 of Compound **6** via the 4-iodophenylalanine derivative **5b**. As illustrated 20 below, this compound can be used directly in a Pd(0) catalyzed coupling reaction with an appropriately substituted boronic acid to form the biaryl compound. Subsequent to any further desired elaborations to attain the desired R^y , the ester is hydrolyzed to give the target compounds **8**. Some -23-

5 biaryl compounds are more accessible by the trimethylstannyl derivative **5c** which can be prepared from **5b** as indicated. Subsequent palladium(II) catalyzed coupling reaction of **5c** with a suitably substituted bromo (or iodo) arene provides the biaryl species **9** which could be further elaborated if needed, to achieve the desired R^y .
 Hydrolysis of the ester gives the target compound **8**.

Scheme 3



10 In the various synthetic methods described above, protection and deprotection of functional groups such as hydroxyl and amino groups may be required. The selection of the appropriate protecting groups, and methods for introducing and removing the protecting groups are within the knowledge of one skilled in the art, and are also 15 described in standard reference books such as Greene and Wuts,

Protective Groups in Organic Synthesis, 2d Ed., John Wiley & Sons, Inc., 1991.

5 The following examples illustrate the preparation of the compounds of Formula I and their incorporation into pharmaceutical compositions and as such are not to be construed as limiting the scope of the invention in any manner.

EXAMPLE 1

10 N-[N-(3,5-Dichlorobenesulfonyl)pyrrole-2-carbonyl-(L)-phenylalanine.

Step A: tert-Butyl pyrrole-2-carboxylate.

At room temperature, to a solution of pyrrole-2-carboxylic acid (500 mg, 4.5 mmol) in anhydrous dichloromethane (5 mL) and anhydrous N,N-dimethylformamide (2.5 mL) was added anhydrous cyclohexane (20 mL). With vigorous stirring, to this clear solution was added (0.85 mL, 1.033 g, 4.73 mmol) of tert-butyl 2,2,2-trichloroacetimidate followed by dropwise addition of boron trifluoride diethyl etherate (170 mL). After stirring at room temperature for 2 hr, additional tert-butyl 2,2,2-trichloroacetimidate (0.85 mL, 1.033 g, 4.73 mmol) and boron trifluoride diethyl etherate (85 mL) were added to the reaction mixture. After stirring at room temperature for an additional 3 hr, additional tert-butyl 2,2,2-trichloroacetimidate (0.85 mL, 1.033 g, 4.73 mmol) and boron trifluoride diethyl etherate (85 mL) were added to the reaction mixture. After stirring at room temperature overnight, the reaction mixture was filtered through a pad of celite, and the residue was washed with ether. The solvent was removed from the filtrate by rotoevaporation and the crude product was purified by flash column chromatography on silica gel eluted with 3-6% ethyl acetate in hexane to give the title compound as a white solid (600 mg, 80% yield), homogeneous by TLC (1/1 hexane/Ethyl acetate).

Mass spectrum (ESI) m/e = 167.1 (M+1)⁺
300 MHz ¹H NMR (CDCl₃) δ 1.57 (s, 9 H), 6.22-6.25 (m, 1 H), 6.83-6.85 (m, 1 H), 6.90-6.92 (m, 1 H), 9.30 (br s, 1H)

Step B: tert-Butyl N-(3,5-dichlorobenzenesulfonyl)pyrrole-2-carboxylate

At room temperature, to a stirred solution of tert-butyl pyrrole-2-carboxylate (obtained from Step A) (120 mg, 0.718 mmol) dissolved in benzene (2.5 mL) was added tetra-N-butylammonium hydrogen sulfate (49 mg, 0.144 mmol) followed by 50% aqueous sodium hydroxide solution (0.72 mL). After 10 min, a solution of 3,5-dichlorobenzenesulfonyl chloride (264 mg, 1.08 mmol) dissolved in benzene (1 mL) was added dropwise via a gas-tight syringe over a 25 min period. The reaction mixture was allowed to stir overnight at room temperature. Ethyl acetate and water were added and the phases were separated. The aqueous layer was re-extracted twice with ethyl acetate and the combined organic layers were washed with water (3X) and dried over anhydrous sodium sulfate. The crude product obtained after filtration and removal of solvents by rotovaporation was purified by flash column chromatography on silica gel eluted with 0.5-2.5% ethyl acetate in hexane to afford the title compound (104 mg), homogeneous by TLC in 10/1 hexane/ethyl acetate; 77% yield, based on starting material consumed) and recovered starting material (58 mg, 50%).

Mass spectrum (ESI) m/e = 375.1 (M+1)⁺
300 MHz ¹H NMR (CDCl₃) δ 1.46 (s, 9 H), 6.32 (t, J = 3.5 Hz, 1H), 6.95 (dd, J = 3.5, 1.9 Hz, 1H), 7.57 (m, 1H), 7.60 (m, 1H), 7.85 (d, J = 1.8, Hz, 1H)

Step C: N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carboxylic acid

At 0°C, to a solution of tert-butyl (N-3,5-dichlorobenzenesulfonyl)-pyrrole 2-carboxylate (obtained from Step B) (88 mg, 0.234 mmol) dissolved in anhydrous dichloromethane (0.2 mL) was added dropwise a 1:1 solution of trifluoroacetic acid and dichloromethane solution (0.4 mL). After 3 minutes, the ice bath was removed and the pinkish reaction mixture was allowed to stir at room temperature for 40 min. The excess trifluoroacetic acid was removed by a stream of nitrogen gas. The residue was dissolved in dichloromethane and methanol and evaporated under reduced pressure and pumped under high vacuum overnight at room temperature. The title compound was obtained (75 mg) as a white solid, homogeneous by

TLC (10% methanol in dichloromethane). This material was used without further purification in the subsequent reaction.

Mass spectrum (ESI) m/e = 318.9 (M+1)⁺

300 MHz ¹H NMR (CDCl₃) δ 2.40 (br s, 1H), 6.37 (d, J = 4.4 Hz, 1H), 7.16

5 (dd, J = 3.6, 1.9 Hz, 1H), 7.56 (t, J = 1.9 Hz, 1H), 7.70 (dd, J = 3.3, 1.9 Hz, 1H), 7.80 (d, J = 1.8 Hz, 2H)

Step D: N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl-(L)-phenylalanine, tert-butyl ester.

10 At room temperature, to a solution of (N-3,5-dichlorobenzenesulfonyl)pyrrole-2-carboxylic acid (obtained from Step C) (40 mg, 0.125 mmol) in dimethylformamide (0.125 mL) was added 1-hydroxybenzotriazole hydrate (19 mg, 0.137 mmol), N-methylmorpholine (35 μL, 32 mg, 0.313 mmol), and (L)-phenylalanine, tert-butyl ester hydrochloride (39 mg, 0.15 mmol). Dimethylformamide was added as required to keep all components in solution. Subsequently, 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (EDC; 29 mg, 0.15 mmol) was added and the reaction mixture was stirred at room temperature for 36 hr. Water was added and the organic layer was extracted with ethyl acetate (3X). The combined organic layers were washed with water (2X), saturated salt solution, and dried over anhydrous sodium sulfate. The solution was filtered and the solvents removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 3-6% ethyl acetate in hexane to afford the title compound (57 mg, 87% yield) as a foam, homogeneous by TLC in 4/1 hexane/ethyl acetate.

Mass spectrum (ESI) m/e = 523.0 (M+1)⁺

400 MHz ¹H NMR (CDCl₃) δ 1.41 (s, 9 H), 3.15 (d, J = 5.0 Hz, 2H), 4.81 (dt,

J = 7.5, 5.6 Hz, 1H), 6.27 (t, J = 3.4 Hz, 1H), 6.48 (d, J = 7.6 Hz, 1H), 6.59

30 (dd, J = 3.6, 1.7 Hz, 1H), 7.14-7.18 (m, 2H), 7.20-7.30 (m, 3H), 7.45 (dd, J = 3.3, 1.7 Hz, 1H), 7.55 (t, J = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 2H)

Step E: N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl-(L)-phenylalanine

35 At 0°C, to a solution of N-[(N-3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-phenylalanine, tert-butyl

ester (8.5 mg, 0.016 mmol) dissolved in anhydrous dichloromethane (50 μ L) was added dropwise 0.085 mL of a 1:1 solution of trifluoroacetic acid/dichloromethane (85 μ L). After stirring for 3 min, the ice bath was removed and the pinkish reaction mixture was stirred at room

5 temperature for 2 hr. The excess trifluoroacetic acid was removed by a stream of nitrogen gas. The residue was taken up in dichloromethane and methanol and rotoevaporated and then pumped overnight under reduced pressure at room temperature. This crude product was

10 purified by flash column chromatography on silica gel eluted with 2-9% methanol in dichloromethane to afford the title compound (6 mg, 80% yield) as a foam, homogeneous by TLC in 10% methanol in dichloromethane.

Mass spectrum (ESI) m/e = 467.1 (M+1)⁺
500 MHz ¹H NMR (CD₃OD) δ 3.06 (dd, J = 14, 8.4 Hz, 1 H), 3.26 (dd, J = 15 14, 5.3 Hz, 1 H), 4.70 (dd, J = 8.4, 5.3 Hz, 1H), 6.33 (t, J = 3.5 Hz, 1H), 6.67 (dd, J = 3.4, 1.6 Hz, 1H), 7.16-7.21 (m, 1H), 7.22-7.28 (m, 4H), 7.57 (dd, J = 3.4, 1.8 Hz, 1H), 7.75 (t, J = 1.9 Hz, 1H), 7.92 (d, J = 1.8 Hz, 2H)

EXAMPLE 2

20

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-homophenylalanine

Step A: N-Carbobenzyloxy-(L)-homophenylalanine, tert-butyl ester

25 At room temperature, to a solution of (N-carbobenzyloxy)-(L)-homophenylalanine (0.476 g, 1.52 mmol) in anhydrous dichloromethane (3.5 mL) was added anhydrous cyclohexane (7 mL). To this clear solution was added with vigorous stirring tert-butyl 2,2,2-trichloroacetimidate (0.30 mL, 1.67 mmol) followed by dropwise addition

30 of boron trifluoride diethyl etherate (30 mL). After stirring at room temperature for 2 hr, additional tert-butyl 2,2,2-trichloroacetimidate (0.45 mL, 2.50 mmol) and boron trifluoride diethyl etherate (45 mL) were added to the reaction mixture and stirring was continued overnight at room temperature. The reaction mixture was filtered through a pad of

35 celite, and the residue was washed with ether. The solvent was removed from the filtrate by rotoevaporation and the crude product was purified

by flash column chromatography on silica gel eluted with 2-6% ethyl acetate in hexane to afford the title compound (211 mg, 38% yield), homogeneous by TLC (4/1 hexane/ethyl acetate).

Mass spectrum (ESI) m/e = 387(M+NH₄)⁺

5 400 MHz ¹H NMR (CDCl₃) δ 1.46 (s, 9H), 1.85-2.00 (m, 1H), 2.08-2.20 (m, 1H), 2.56-2.73 (m, 2H), 4.28-4.35 (m, 1H), 5.33 (br d, 1H), 7.10-7.23 (m, 3H), 7.23-7.40 (m, 7 H)

Step B: (L)-Homophenylalanine, tert-butyl ester

10 A solution of (N-carbobenzyloxy)-(L)-homophenylalanine, tert-butyl ester (100 mg, 0.281 mmol) in anhydrous ethanol (2 mL) and anhydrous ethyl acetate (2 mL) was degassed and the reaction flask filled with hydrogen. 10% Palladium on carbon catalyst (25 mg) was added and the mixture was hydrogenated under a balloon of hydrogen at 15 room temperature for 2.3 hr. The catalyst was removed by filtration through a pad of celite, and solvent was removed from the filtrate by rotovaporation. After pumping under reduced pressure at room temperature, the material thus obtained (homogeneous by TLC in 4/1 hexane / ethyl acetate) was used in the subsequent reaction without 20 further purification.

mass spectrum (ESI) m/e = 222 (M+1)⁺.

400 MHz ¹H NMR (CD₃OD) δ 1.55 (s, 9H), 2.05-2.25 (m, 2H), 2.68-2.75 (m, 1H), 2.75-2.85 (m, 1H), 3.90(t, J = 6.3 Hz, 1H), 7.22-7.25 (m, 3H), 7.25-7.33 (m, 2 H)

25 Step C: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]- (L)-homophenylalanine

The title compound was prepared in two steps from N-(3,5-dichlorobenzenesulfonyl)pyrrole-2-carboxylic acid (obtained from Example 1, Step C) and (L)-homophenylalanine, tert-butyl ester (obtained from Step B) as described in Example 1 Steps D and E. This provided the title compound in 67% yield (last step), homogeneous by TLC (10% methanol in dichloromethane).

30 mass spectrum (ESI) m/e = 481.3 (M+1)⁺

35 400 MHz ¹H NMR (CD₃OD) δ 2.05-2.12 (m, 1H), 2.18-2.25 (m, 1H), 2.68-2.85 (m, 2H), 4.45 (dd, J = 7.0, 4.0 Hz, 1H), 6.40 (t, J = 3.4 Hz, 1H), 6.84

(dd, $J = 3.6, 1.7$ Hz, 1H), 7.12-7.20 (m, 1H), 7.21-7.27 (m, 4 H), 7.62 (dd, $J = 3.3, 1.7$ Hz, 1H), 7.77 (t, $J = 1.8$ Hz, 1H), 7.98 (d, $J = 1.9$ Hz, 1H)

EXAMPLE 3

5

N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl]-L-norleucine

The title compound was prepared in 91% yield as described for N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-homophenylalanine in Example 2 except that (L)-norleucine, tert-butyl ester was used instead of (L)-homophenylalanine, tert-butyl ester. The title compound was homogeneous by TLC (10% methanol in dichloromethane).

Mass spectrum (ESI) m/e = 433.1 (M+1)⁺
15 400 MHz ¹H NMR (CD₃OD) δ 0.92 (t, $J = 7.1$ Hz, 3H), 1.35-1.50 (m, 4H), 1.68-1.80 (m, 1H), 1.85-2.00 (m, 1H), 4.31 (dd, $J = 4.6, 3.8$ Hz, 1H), 6.38 (t, $J = 3.4$ Hz, 1H), 6.85 (dd, $J = 3.5, 1.7$ Hz, 1H), 7.59 (dd, $J = 3.3, 1.7$ Hz, 1H), 7.79 (t, $J = 1.8$ Hz, 1H), 7.96 (d, $J = 1.8$ Hz, 2H)

20

EXAMPLE 4

N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl]-L-O-tert-butyl-tyrosine

25 Step A: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-O-tert-butyl-tyrosine, methyl ester

The title compound was prepared in 73% yield according to Example 1, Step D except that (L)-O-tert-butyl-tyrosine, methyl ester was used instead of (L)-phenylalanine, tert-butyl ester.

30 Mass spectrum (ESI) m/e = 553.4 (M+1)⁺
400 MHz ¹H NMR (CDCl₃) δ 1.30 (s, 9H), 3.10-3.20 (m, 2H), 3.72 (s, 3H), 4.88-4.95 (m, 1H), 6.26 (t, $J = 3.5$ Hz, 1H), 6.40-6.45 (d, $J = 7.5$ Hz, 1H), 6.56 (dd, $J = 3.5, 1.7$ Hz, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.98 (d, $J = 8.6$ Hz, 2H), 7.44 (dd, $J = 3.3, 1.7$ Hz, 1H), 7.56 (t, $J = 1.8$ Hz, 1H), 7.91 (d, $J = 1.8$ Hz, 2H)

35 2H)

Step B: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-
(L)-O-tert-butyl-tyrosine
At 0°C, to a solution of N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-
(L)-O-tert-butyl-tyrosine,
5 methyl ester (50 mg, 0.0903 mmol) in ethanol (0.6 mL) was added
dropwise over 20 minutes via a gastight syringe, an aqueous solution of
0.2N sodium hydroxide (0.452 mL) in ethanol (2 mL). After 1 hr, the
reaction mixture was diluted with ethyl acetate and acidified with 5%
10 citric acid to pH 3-4. After separation of the organic layer, the aqueous
phase was re-extracted with ethyl acetate (3X). The combined organic
layers were washed with water and saturated salt solution and dried
over anhydrous magnesium sulfate. The mixture was filtered and the
solvents removed by rotovaporation. The crude product was purified via
a Chromatotron (1000 μ plate, gradient elution using 1-10%
15 methanol/dichloromethane) to afford the title product (25 mg) and
recovered starting ester (25 mg).
Mass spectrum (ESI) m/e = 539.6 (M+1)⁺
400 MHz ¹H NMR (CD₃OD) δ 1.27 (s, 9H), 2.95-3.15 (m, 1H), 3.20-3.40 (m,
1H), 4.55-4.70 (m, 1H), 6.32 (d, J = 1.2 Hz, 1H), 6.66 (dd, J = 4.7, 2.6 Hz,
20 1H), 6.86 (br s, 3H), 7.05-7.25 (m, 2H), 7.57 (d, J = 3.2 Hz, 1H), 7.78 (s, 1H),
7.94 (br s, 2H)

EXAMPLE 5

25 N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-
(L)-O-benzyl-
tyrosine

Step A: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-
(L)-
tyrosine, methyl ester
30 At 0°C, to a stirred solution of N-[N-(3,5-dichlorobenznesulfonyl-2-carbonyl)pyrrole]-
(L)-O-tert-butyl-tyrosine, methyl ester (obtained from Example 4, Step A) (0.344 g, 0.622 mmol) in
dichloromethane (1 mL) was added dropwise a 1:1 (v/v) solution of
trifluoroacetic acid/dichloromethane (0.958 mL). The reaction mixture
35 was allowed to warm up to room temperature slowly and stirred for a
total of 4 hr. The excess trifluoroacetic acid was removed by a stream of

nitrogen gas and the residue was coevaporated with dichloromethane and then pumped under reduced pressure overnight to give the title compound (316 mg, 95%) as a foam, homogeneous by TLC (1/1 hexane / ethyl acetate). This material was used in the subsequent reaction

5 without further purification.

Mass spectrum (ESI) m/e = 497.5 (M+1)⁺

400 MHz ¹H NMR (CDCl₃) δ 1.9-2.7 (br s, 1H), 3.10-3.15 (m, 2H), 3.74 (s, 3H), 4.90 (m, 1H), 6.28 (t, J = 3.4 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 6.60 (dd, J = 3.5, 1.7 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 7.45

10 (dd, J = 3.3, 1.6 Hz, 1H), 7.56 (t, J = 1.8 Hz, 1H), 7.89 (d, J = 1.8 Hz, 2H)

Step B: N-[N-(3,5-Dichlorobzenzesulfonyl)pyrrole-2-carbonyl]-L-O-benzyl-tyrosine, methyl ester

A mixture of N-[N-(3,5-dichlorobzenzesulfonyl)pyrrole-2-carbonyl]-L-tyrosine, methyl ester (90 mg, 0.18mmol), benzyl bromide (123 mg, 0.72 mmol), powdered anhydrous potassium carbonate (150 mg; 1.09 mmol) in dimethylformamide (3 mL) was stirred overnight at 40°C. Acetic acid was added to pH 4-5 and the reaction mixture extracted with ethyl acetate (4X). The combined organic layers were washed with water and saturated salt solution and dried over anhydrous magnesium sulfate. The mixture was filtered and the solvents were removed rotovaporation. The crude product was purified via Chromatotron (gradient elution using hexane/ethyl acetate) to afford the title compound (12.4 mg), homogeneous by TLC in 1/1 hexane/ethyl acetate), and

20 recovered starting material (46 mg).

Mass spectrum (ESI) m/e = 587.4 (M+1)⁺

400 MHz ¹H NMR (CDCl₃) δ 3.08-3.20 (m, 2H), 3.74 (s, 3H), 4.88-4.96 (m, 1H), 5.01 (s, 2H), 6.27 (d, J = 3.4 Hz, 1H), 6.44 (d, J = 7.9 Hz, 1H), 6.58 (dd, J = 3.6, 1.8 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.25

25 7.46 (m, 6H), 7.56 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 1.8 Hz, 2H)

Step C: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-O-benzyl-tyrosine

To a stirred solution of N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-O-benzyl-tyrosine, methyl ester (12.4 mg, 0.021 mmol), in ethanol (0.5 mL) at 0°C, was added

dropwise over 10 minutes via a gastight syringe a solution of aqueous 0.2N sodium hydroxide (0.106 mL) in ethanol (1 mL). The reaction mixture was slowly warmed up to room temperature. After stirring for 6.5 hr, the reaction mixture was diluted with ethyl acetate and water in 5 the cold, and acidified with 1.0N acetic acid to pH 4-5. After separation of the layers, the aqueous phase was re-extracted with ethyl acetate (3X). The combined organic layers were washed with water and saturated salt solution and dried over anhydrous magnesium sulfate. The mixture was filtered and the solvent removed by rotoevaporation. The crude 10 product was purified via a Chromatotron (1000 μ plate, gradient elution using 1-10% methanol/dichloromethane) to afford the title product (1.2 mg).
Mass spectrum (ESI) m/e = 590.41 (M+NH₄)⁺
500 MHz ¹H NMR (CD₃OD) δ 3.01 (dd, J = 13.9, 7.7 Hz, 1H), 3.3.18 (dd, J = 13.9, 5.3 Hz, 1H), 4.62 (m, 1H), 5.02 (s, 2H), 6.33 (d, J = 3.4 Hz, 1H), 6.67 15 (dd, J = 3.4, 1.6 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.25-7.44 (m, 5H), 7.57 (dd, J = 3.2, 1.6 Hz, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 2H)

20

EXAMPLE 6N-[N-(3,5-Dichlorobzenzenesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-methoxyphenyl)phenylalanine

25 Step A: N-Butoxycarbonyl-L-4-iodophenylalanine tert-butyl ester
To a solution of N-butoxycarbonyl-(L)-4-iodophenylalanine (1.00 g, 2.56 mmol) in anhydrous dichloromethane (5 mL) and anhydrous dimethylformamide (0.5 mL) at room temperature was added anhydrous cyclohexane (14 mL). To this clear solution with vigorous 30 stirring was added tert-butyl 2,2,2-trichloroacetimidate (0.482 mL, 0.588 g, 2.69 mmol) followed by dropwise addition of boron trifluoride diethyl etherate (75 mL). After stirring at room temperature for 2 hr, additional tert-butyl 2,2,2-trichloroacetimidate (0.482 mL, 0.588 g, 2.69 mmol) and boron trifluoride diethyl etherate (75 mL) were added to the reaction 35 mixture and stirring was continued overnight at room temperature. The reaction mixture was filtered through a pad of celite, and the

residue was washed with ether. The solvents were removed by rotovaporation and the crude product was purified by flash column chromatography through silica gel eluted with 2-6% ethyl acetate in hexane to afford the title compound (840 mg, 73% yield) as an oil,
5 homogeneous by TLC (6/1 hexane/Ethyl acetate).
Mass spectrum (ESI) m/e = 448.5 (M+1)
400 MHz ¹H NMR (CDCl₃) δ 1.39 (s, 9H), 1.40(s, 9H), 2.90-3.18 (m, 2H),
4.40 (dd, J = 7.8, 3.6 Hz, 1H), 4.95-5.02 (br d, 1H), 6.89(d, J = 8.4 Hz, 2H),
7.58 (d, J = 8.4 Hz, 2H)
10
Step B: (L)-4-iodophenylalanine, tert-butyl ester hydrochloride
N-butoxycarbonyl-(L)-4-iodophenylalanine (723 mg, 1.62
mmol) was dissolved in anhydrous ethyl acetate (0.5 mL) at room
temperature and then cooled to 0°C. 1N Hydrochloric acid in ethyl
15 acetate (4.0 mL) was added dropwise and the ice bath removed 30
minutes after completion of the addition. The reaction mixture was
allowed to stir at room temperature overnight. Additional 1N
Hydrochloric acid in ethyl acetate (4.0 mL) was added and the mixture
allowed to stir for another 24 hr. Solvents were removed rotovaporation
20 and the resulting white powder was dried overnight under reduced
pressure at room temperature to afford the title compound (610 mg, 98%
yield), homogeneous by TLC (10% methanol/dichloromethane) which
was used in subsequent reactions without further purification.
Mass spectrum (ESI) m/e = 348.2 (M+1)
25 400 MHz ¹H NMR (CD₃OD) δ 1.41(s, 9H), 3.11 (d, J = 6.6 Hz, 2H), 4.15 (t, J
= 6.6 Hz, 1H), 7.07 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 7.9 Hz, 2H)

Step C: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]- (L)-
4-iodophenylalanine, tert-butyl ester
30 The title compound was prepared from (N-3,5-
dichlorobenzenesulfonyl)pyrrole-2-carboxylic acid (obtained from
Example 1, Step C) and (L)-4-iodophenylalanine, tert-butyl ester
hydrochloride (obtained from Step B) according to the procedure of
Example 1, Step D. A 72% yield of the title compound was obtained after
35 chromatographic purification.
Mass spectrum (ESI) m/e = 649.3(M+1)

500 MHz ^1H NMR (CDCl_3) δ 1.46 (s, 9H), 3.10-3.20 (m, 2H), 4.81 (dd, J = 12.1, 5.9 Hz, 1H), 6.32 (t, J = 3.2 Hz, 1H), 6.52 (d, J = 7.3 Hz, 1H), 6.64 (dd, J = 3.4, 1.8 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 7.49 (dd, J = 3.0, 1.4 Hz, 1H), 7.60 (m, 1H), 7.62 (d, J = 8.1 Hz, 2H), 7.95 (d, J = 1.6 Hz, 2H)

5

Step D: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl-(L)-4-(2-methoxyphenyl)phenylalanine, tert-butyl ester

A mixture of 2-methoxybenzene boronic acid (13 mg, 0.085 mmol) and 2.0N aqueous sodium carbonate (89 μL) in anhydrous ethanol (0.13 mL) was stirred vigorously at room temperature for 30 minutes. More anhydrous ethanol (0.12 mL) was added and stirring continued for 5 min. To this slurry was added of N-[N-(3,5-dichlorobenzenesulfonyl)pyrrole-2-carbonyl-(L)-4-iodophenylalanine, tert-butyl ester (obtained from Step C) (46 mg, 0.071 mmol). This mixture was degassed and filled with dry nitrogen three times. Tetrakis(triphenylphosphine)palladium(0) (8.2 mg, 0.0071 mmol) was added and the flask degassed/filled with dry nitrogen twice. The reaction mixture was heated in an oil bath to 60°C for 6 hr. After cooling to room temperature, the solvents were removed by rotoevaporation and the residue was dissolved in 5% aqueous sodium carbonate, then extracted with ethyl acetate (3X). The combined organic layers were washed with water and saturated salt solution and dried over anhydrous sodium sulfate. The mixture was filtered and the solvents removed from the filtrate by rotoevaporation. The crude product was purified by flash column chromatography through silica gel eluted with 2-6% ethyl acetate in hexane to afford the title compound (40 mg, 89% yield) as an off-white foam.

Mass spectrum (ESI) m/e = 646.6 (M+NH₄).

400 MHz ^1H NMR (CDCl_3) δ 1.42 (s, 9H), 3.19 (t, J = 5.1 Hz, 2H), 3.77 (s, 3H), 4.80-4.88 (m, 1H), 6.27 (t, J = 3.5 Hz, 1H), 6.52 (d, J = 7.4 Hz, 1H), 6.61 (dd, J = 3.6, 1.8 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 7.00 (dt, J = 7.4, 1.0 Hz, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.42-7.46 (m, 3H), 7.55 (t, J = 1.8 Hz, 1H), 7.94 (d, J = 1.8 Hz, 2H)

35

Step E: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl-(L)-4-(2-methoxyphenyl)phenylalanine

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-4-(2-methoxyphenyl)phenylalanine, tert-butyl ester (obtained from Step D) was treated with trifluoroacetic acid/dichloromethane according to Example 1, Step E to afford the title compound in 58% yield as a white 5 foam, homogeneous by TLC (10% methanol/dichloromethane).
 Mass spectrum (ESI) m/e = 573.4 (M+1).
 500 MHz ^1H NMR (CD₃OD) δ 3.16 (m, 1H), 3.28 (m, 1H), 3.69 (s, 3H), 4.60 (m, 1H), 6.26 (t, J = 3.5 Hz, 1H), 6.64 (dd, J = 3.7, 1.7 Hz, 1H), 6.92 (dt, J = 7.3, 0.7 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.16 (dd, J = 7.5, 1.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.24 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.50 (dd, J = 3.1, 1.6 Hz, 1H) 7.64 (t, J = 1.8 Hz, 1H), 7.91 (d, J = 1.8 Hz, 2H)

EXAMPLE 7

15 N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-(4-(3-methoxyphenyl)phenylalanine

The title compound was prepared as described for N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-(4-(2-methoxyphenyl)phenylalanine in Example 5 except that 3-methoxybenzene boronic acid was used instead of 2-methoxybenzene boronic acid. The title compound was homogeneous by TLC (10% methanol/dichloromethane) and obtained in a 26% yield.

Mass spectrum (ESI) m/e = 573.4 (M+1).
 25 500 MHz ^1H NMR (CD₃OD) δ 3.12 (dd, J = 13.7, 7.1 Hz, 1H), 3.29 (dd, J = 13.9, 5.0 Hz, 1H), 3.80 (s, 3H), 4.62 (m, 1H), 6.30 (t, J = 3.2 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.2, 2.7 Hz, 1H), 7.05 (br s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.26 (m, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.54 (br s, 1H) 7.68 (t, J = 1.0 Hz, 1H), 7.91 (d, J = 1.0 Hz, 2H)

30

EXAMPLE 8

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-(4-(2-cyanophenyl)phenylalanine

35

Step A: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-4-(trimethyltin)phenylalanine, tert-butyl ester

A mixture of N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-4-iodophenylalanine, tert-butyl ester (obtained from Example 5 Step C) (400 mg, 0.616 mmol), dry 1,4-dioxane (4 mL), lithium chloride (29 mg, 0.68 mmol), and triphenylphosphine (3.2 mg, 0.012 mmol) at room temperature was degassed and filled with dry nitrogen (4X). Under dry nitrogen, hexamethylditin (166 μ L, 0.862 mmol) was added and the mixture was again degassed and filled with dry nitrogen (3X) before tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol) was added. The resulting yellow reaction mixture was stirred in an oil bath at 95°C and for 2.5 hr. After cooling to room temperature, the reaction mixture was dissolved in ethyl acetate (30 mL) and washed with 5% sodium bicarbonate solution (2 x 5 mL) and saturated salt solution (2 x 5 mL), and dried over anhydrous magnesium sulfate. The mixture was filtered and the solvent was removed by rotovaporation. The crude product was purified by flash column chromatography through silica gel eluted with 2-6% ethyl acetate in hexane to afford the title compound (344 mg, 81% yield) as a wet yellow solid, homogeneous by TLC (5/1 hexane/Ethyl acetate) after pumping in vacuo overnight.

Mass spectrum (ESI) m/e = 687.5 (M+1).
400 MHz 1 H NMR (CDCl₃) δ 0.25 (s, 9H), 1.42 (s, 9H), 3.13 (d, J = 5.5 Hz, 2H), 4.79 (m, 1H), 6.27 (t, J = 3.5 Hz, 1H), 6.46 (d, J = 7.7 Hz, 1H), 6.59 (dd, J = 3.4, 1.5 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.45 (dd, J = 3.2, 1.8 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 2H)

Step B: N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl]-L-4-(2-cyanophenyl)phenylalanine, tert-butyl ester

A solution of N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl]-L-4-(trimethyltin)phenylalanine, tert-butyl ester (obtained from Step A) (100 mg, 0.146 mmol) and 2-bromobenzonitrile (40 mg, 0.219 mmol) in anhydrous toluene (4 mL) was degassed and filled with dry nitrogen (4X) before dichlorobis(triphenylphosphine)palladium(II) (4.10 mg, 0.0584 mmol) was added. The resulting mixture was again degassed and filled with dry nitrogen (2X) before being placed in a pre-heated oil bath at 100°C for 4 hr. After cooling to room temperature, the

reaction mixture was diluted with ethyl acetate and washed with 5% sodium bicarbonate solution (2X). The combined organic layers were washed with saturated salt solution (2X), and dried over anhydrous sodium sulfate. The mixture was filtered and the solvents removed by 5 rotovaporation. The crude product was purified by flash column chromatography through silica gel eluted with 2-6% ethyl acetate in hexane to afford the title compound (75 mg, 82 % yield) as a white foam, homogenous by TLC (2/1 hexane/ethyl acetate);
 Mass spectrum (ESI) m/e = 641.5 (M+NH₄).
 10 400 MHz ¹H NMR (CDCl₃) δ 1.42 (s, 9H), 3.23 (d, J = 5.8 Hz, 2H), 4.82-4.90 (m, 1H), 6.28 (t, J = 3.5 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H), 6.63 (dd, J = 3.6, 1.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.41 (dt, J = 7.6, 1.2 Hz, 1H), 7.45 (dd, J = 3.3, 1.7 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.49 (m, 1H), 7.56 (t, J = 1.8 Hz, 1H), 7.60 (dt, J = 7.7, 1.4 Hz, 1H), 7.74 (dd, J = 7.7, 1.4 Hz, 1H), , 15 7.93 (d, J = 1.8 Hz, 2H)

Step C: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl-(L)-(4-(2-cyanophenyl)phenylalanine
N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-4-(2-cyanophenyl)phenylalanine,
 20 (2-cyanophenyl)phenylalanine, tert-butyl ester (obtained from Step B) was treated with trifluoroacetic acid/dichloromethane according to Example 1, Step E to afford the title compound in 91% yield as a white foam, homogeneous by TLC (10% methanol/dichloromethane).
 Mass spectrum (ESI) m/e = 585.4 (M+NH₄).
 25 400 MHz ¹H NMR (CD₃OD) δ 3.18 (dd, J = 13.7, 7.0 Hz, 1H), 3.33 (m, 1H), 4.62 (m, 1H), 6.31 (t, J = 3.4 Hz, 1H), 6.68 (dd, J = 3.5, 1.7 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.38 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.48 (dt, J = 7.6, 1.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.56 (dd, J = 3.2, 1.7 Hz, 1H), 7.67 (dt, J = 7.7, 1.3 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 7.78 (d, J = 7.7, 1H), 7.95 (d, J = 2.0 Hz, 2H)

EXAMPLE 9

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl-(L)-(4-(3-cyanophenyl)phenylalanine

The title compound was prepared as described for N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-cyanophenyl)phenylalanine in Example 7 except that 3-bromobenzonitrile was used instead of 2-bromobenzonitrile. The title compound was homogeneous by TLC (10% methanol/dichloromethane) and obtained in a 91% yield.

5 Mass spectrum (ESI) m/e = 567.5 (M+1).
10 400 MHz 1 H NMR (CD₃OD) δ 3.15 (dd, J = 13.5, 6.8 Hz, 1H), 3.33 (m, 1H), 4.65 (m, 1H), 6.33 (t, J = 3.5 Hz, 1H), 6.71 (dd, J = 3.7, 1.8 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.56-7.60 (m, 2H), 7.64 (td, J = 7.8, 1.4 Hz, 1H), 7.71 (t, J = 2.0 Hz, 1H), 7.87 (td, J = 7.9, 1.3 Hz, 1H), 7.90 (m, 2H), 7.91 (d, J = 2.0 Hz, 2H)

EXAMPLE 10

15

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-propyloxyphenyl)phenylalanine

The title compound was prepared as described for N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-cyanophenyl)phenylalanine in Example 7 except that 2-propoxybromobenzene (obtained from the corresponding phenol by treatment with potassium carbonate and iodopropane) was used instead of 2-bromobenzonitrile. The title compound was homogeneous by TLC (10% methanol/dichloromethane) and obtained in a 37% yield.

25 Mass spectrum (ESI) m/e = 601 (M+1).
30 500 MHz 1 H NMR (CD₃OD) δ 0.87 (t, J = 7.3 Hz, 3H), 1.63 (m, 2H), 3.15 (m, 2H), 3.86 (t, J = 6.4 Hz, 2H), 4.68 (dd, J = 5.0, 7.5 Hz, 1H), 6.30 (m, 1H), 6.64 (m, 1H), 6.92 (m, 1H), 7.18-7.44 (m, 5H), 7.45-7.57 (m, 2H), 7.70 (m, 1H), 7.87 (td, J = 7.9, 1.3 Hz, 1H), 7.91 (m, 1H), 7.93 (d, J = 1.8 Hz, 2H)

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EXAMPLE 11

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-tetrazolylphenyl)phenylalanine.

35

Step A: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-
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(4-(2-tetrazolylphenyl)phenylalanine t-butyl ester
N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-
(4-(2-cyanophenyl)phenylalanine t-butyl ester (44 mg, 0.070 mmol,
obtained from Example 8, Step B) was dissolved in toluene and 66 mg
5 (0.32 mmol) of trimethyltin azide was added. The mixture was stirred
and refluxed for 36 h. TLC (2:1 hexane/ethyl acetate) indicated
disappearance of most of starting material. After being cooled to room
temperature, volatiles were removed and the residue was triburated
with ether. The ether -insoluble portion was taken up in 3 mL of
10 methanol and stirred with 1 g silica gel overnight at room temperature.
The methanol was carefully removed and the crude product thus
obtained was flash chromatographed over 10 mL silicq gel, (eluting with
1-2-5-7-10% methanol/dichloromethane) to give 12 mg of a gum,
homogeneous by TLC (10% methanol/methylene chloride)
15 Mass spectrum (ESI) m/e = 667.0 (M+H).
400 MHz ¹H NMR (CDCl₃) δ 1.49 (s, 9H), 2.93 (dd, J=13.6, 7.8 Hz), 1H),
3.30 (m, 1H), 4.89-4.95 (m, 1H), 6.31 (m, 1H), 6.69 (m, 1H), 6.77 (d, J = 8.0
Hz, 1H), 7.13 (m, 2H), 7.24 (m, 2H), 7.40-7.60 (m, 4H), 7.82 (s, 2H), , 8.06-
8.18 (m, 1H)
20
Step B: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-
(4-(2-tetrazolylphenyl)phenylalanine
N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-
(4-(2-tetrazolylphenyl)phenylalanine t-butyl ester (obtained from Step A)
25 was treated with trifluoroacetic acid/dichloromethane according to
Example 1, Step E to afford the title compound in 50% yield as a white
foam, homogeneous by TLC (10% methanol/dichloromethane).
Mass spectrum (ESI) m/e = 611 (M+H).
500 MHz ¹H NMR (CD₃OD) δ 3.07 (dd, J = 13.8.7Hz, 1H), 3.27 (m, 1H),
30 4.72 (dd, J = 5.1, 8.7 Hz, 1H), 6.37 (t, J = 3.4 Hz, 1H), 6.64 (dd, J = 3.7, 1.9
Hz, 1H), 7.04 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.40-7.80 (m, 5H),
7.94 (d, J = 1.8 Hz, 2H)

EXAMPLE 12

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-methylthiophenyl)phenylalanine

The title compound was prepared as described for N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-cyanophenyl)phenylalanine in Example 7 except that 2-bromothioanisole) was used instead of 2-bromobenzonitrile. The title compound was homogeneous by TLC (10% methanol/dichloromethane) and obtained in a 45% yield.

10 Mass spectrum (ESI) m/e = 606 (M+NH₄).
 500 MHz ¹H NMR (CD₃OD) δ 2.27 (s, 3H), 3.15 (dd, J = 13.7, 7.1 Hz, 1H), 3.35 (m, 1H), 4.63 (m, 1H), 6.32 (t, J = 3.5 Hz, 1H), 6.67 (m, 1H), 7.0-7.2 (m, 3H), 7.2-7.5 (m, 5H), 7.54 (t, J = 1.4 Hz, 1H), 7.75 (m, 1H), 7.95 (d, J = 1.8 Hz, 2H)

15

EXAMPLE 13

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-methylsulfonylphenyl)phenylalanine

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Step A: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-methylthiophenyl)phenylalanine, t-butyl ester

The title compound was prepared as described for N-[N-(3,5-dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-cyanophenyl)phenylalanine t-butyl ester in Example 7 Step A except that 2-bromothioanisole) was used instead of 2-bromobenzonitrile. The title compound was homogeneous by TLC (5:1 hexane/ethyl acetate) and obtained in a 5% yield.

Mass spectrum (ESI) m/e = 645 (M+H).
 30 500 MHz ¹H NMR (CDCl₃) δ 1.43 (s, 9H), 2.32 (s, 3H), 3.22 (d, J = 5.8 Hz, 2H), 4.84 (dd, J = 1.7, 5.8 Hz, 1H), 6.27 (t, J = 3.4 Hz, 1H), 6.53 (d, J=7.6 Hz, 1H), 6.61 (dd J = 1.7,3.6 Hz, 1H), 7.15-7.4 (m, 8H), 7.45 (dd, J = 1.7, 3.3 Hz, 1H), 7.55 (t, J = 2.1 Hz, 1H), 7.94 (d, J = 1.8 Hz, 2H)

35 Step B: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-(2-methylsulfonylphenyl)phenylalanine t-butyl ester

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-(4-(2-methylthiophenyl)phenylalanine t-butyl ester (15 mg, 0.023 mmol) was dissolved in 0.100 mL of dichloromethane and cooled to 0°C. m-Chloroperbenzoic acid (8.6 mg, 0.046 mmol) was added and the ice-bath was removed. After being stirred at room temperature for 3 h, the reaction mixture was diluted with methylene chloride and washed with 5% aqueous sodium bicarbonate. The phases were separated and the aqueous phase was reextracted with methylene chloride twice more. The organic layers were combined and washed with brine and dried over anhydrous sodium sulfate. The residue obtained after filtration and removal of volatiles was flashed chromatographed to give 7 mg (44%) of the desired product, cleanly. Homogeneous by TLC (2:1 hexane/ethyl acetate)

Mass spectrum (ESI) m/e = 674.3 (M+NH₄).

500 MHz ¹H NMR (CDCl₃) δ 1.49 (s, 9H), 2.58 (s, 3H), 3.21 (dd, J = 5.3, 14 Hz, 1H), 3.32 (dd, J = 5.9, 14 Hz, 1H), 4.89 (dd, J = 5.7, 13 Hz, 1H), 6.82 (t, J = 3.4 Hz, 1H), 6.65 (d, J=7.3 Hz, 1H), 6.69 (dd J = 1.6,3.4 Hz, 1H), 7.25-7.65 (m, 5H), 7.65-7.70 (m, 3H), 7.97 (d, J = 1.9 Hz, 2H), 8.24 (dd, J = 1.1, 8.0 Hz, 1H)

Step C: N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-(4-(2-methylsulfonylphenyl)phenylalanine

N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-(L)-(4-(2-methylsulfonylphenyl)phenylalanine t-butyl ester (obtained from Step B) was treated with trifluoroacetic acid/dichloromethane according to Example 1, Step E to afford the title compound in 65% yield as a white foam, homogeneous by TLC (10% methanol/dichloromethane).

Mass spectrum (ESI) m/e = 638 (M+NH₄).

500 MHz ¹H NMR (CD₃OD) δ 2.49 (s, 3H), 3.14 (dd, J = 13.7, 5.7 Hz, 1H), 3.36 (m, 1H), 4.65 (m, 1H), 6.34 (t, J = 3.4 Hz, 1H), 6.73 (dd, J = 3.7, 1.7 Hz, 1H), 7.30-7.50 (m, 5H), 7.55-7.95 (m, 4H), 7.96 (d, J = 1.8 Hz, 2H), 8.12 (dd, J = 1.2, 7.9 Hz, 1H)

EXAMPLE 14

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N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl]-(L)-tyrosine

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Step A: N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl-(L)-(4-t-butyl)tyrosine t-butyl ester
N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carboxylic acid

5 (obtained from Example 1, Step C) was coupled with tyrosine t-butyl ether t-butyl ester hydrochloride according to the procedure of Example 1, Step D to afford the title compound in 60% yield as a white foam, homogeneous by TLC (4:1 hexane/ethyl acetate).

Mass spectrum (ESI) m/e = 612 (M+NH₄).

10 400 MHz ¹H NMR (CDCl₃) δ 1.30 (s, 9H), 1.39 (s, 9H), 3.10 (d, J = 5.9 Hz, 2H), 4.76 (dd, J=1.7, 5.9 Hz, 1H), 6.26 (t, J = 3.4 Hz, 1H), 6.48 (d, J=7.7 Hz, 1H), 6.57 (dd, J = 3.5, 1.5 Hz, 1H), 6.88 (dd, J = 6.6, 2.0 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.44 (dd, J= 3.3, 1.4Hz, 1H), 7.55 (t, J = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 2H)

15

Step B: N-[N-(3,5-Dichlorobenzenesulfonyl)pyrrole-2-carbonyl-(L)-tyrosine
N-[N-(3,5-Dichlorobenznesulfonyl)pyrrole-2-carbonyl]-L-(4-t-butyl)tyrosine t-butyl ester (obtained from Step A) was treated with

20 trifluoroacetic acid/dichloromethane according to Example 1, Step E to afford the title compound in 25% yield as an orange solid, homogeneous by TLC (10% methanol/dichloromethane).

Mass spectrum (ESI) m/e = 500 (M+NH₄).

400 MHz ¹H NMR (CD₃OD) δ 2.97 (dd, J = 13, 7.4 Hz, 1H), 3.15 (dd, J=13, 5.3 Hz, 1H), 4.51 (dd, J=7.4, 5.3 Hz, 1H), 6.34 (t, J = 3.4 Hz, 1H), 6.66 (m, 3H), 7.04 (m, 2H), 7.58 (dd, J=1.6, 3.3 Hz, 1H), 7.78 (m, 1H), 7.94 (d, J = 1.4 Hz, 2H)

EXAMPLE 15

30 Inhibition of VLA-4 Dependent Adhesion to BSA-CS-1 Conjugate

Step A. Preparation of CS-1 Coated Plates.
Untreated 96 well polystyrene flat bottom plates were coated

35 with bovine serum albumin (BSA; 20 µg/ml) for 2 hours at room temperature and washed twice with phosphate buffered saline (PBS).

The albumin coating was next derivatized with 10 µg/ml 3-(2-pyridyldithio) propionic acid N-hydroxysuccinimide ester (SPDP), a heterobifunctional crosslinker, for 30 minutes at room temperature and washed twice with PBS. The CS-1 peptide (Cys-Leu-His-Gly-Pro-Glu-Ile-
5 Leu-Asp-Val-Pro-Ser-Thr), which was synthesized by conventional solid phase chemistry and purified by reverse phase HPLC, was next added to the derivatized BSA at a concentration of 2.5 µg/ml and allowed to react for 2 hours at room temperature. The plates were washed twice with PBS and stored at 4°C.

10

Step B. Preparation of Fluorescently Labeled Jurkat Cells.

Jurkat cells, clone E6-1, obtained from the American Type Culture Collection (Rockville, MD; cat # ATCC TIB-152) were grown and maintained in RPMI-1640 culture medium containing 10% fetal calf serum (FCS), 50 units/ml penicillin, 50 µg/ml streptomycin and 2 mM glutamine. Fluorescence activated cell sorter analysis with specific monoclonal antibodies confirmed that the cells expressed both the $\alpha 4$ and $\beta 1$ chains of VLA-4. The cells were centrifuged at 400xg for five minutes and washed twice with PBS. The cells were incubated at a concentration of 2×10^6 cells/ml in PBS containing a 1 µM concentration of a fluorogenic esterase substrate (2', 7-bis-(2-carboxyethyl)-5-(and -6)-carboxyfluorescein, acetoxyethyl ester; BCECF-AM; Molecular Probes Inc., Eugene, Oregon; catalog #B-1150) for 30-60 minutes at 37°C in a 5% CO₂/air incubator. The fluorescently labeled Jurkat cells were washed
15 two times in PBS and resuspended in RPMI containing 0.25% BSA at a
20 final concentration of 2.0×10^6 cells/ml.
25

Step C. Assay Procedure.

Compounds of this invention were prepared in DMSO at
30 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100µM. Three µL of diluted compound, or vehicle alone, were premixed with 300 µL of cell suspension in 96-well polystyrene plates with round bottom wells. 100 µL aliquots of the cell /compound mixture were then transferred in
35 duplicate to CS-1 coated wells. The cells were next incubated for 30 minutes at room temperature. The non-adherent cells were removed by
44

two gentle washings with PBS. The remaining adherent cells were quantitated by reading the plates on a Cytofluor II fluorescence plate reader (Perseptive Biosystems Inc., Framingham, MA; excitation and emission filter settings were 485 nm and 530 nm, respectively). Control 5 wells containing vehicle alone were used to determine the level of cell adhesion corresponding to 0% inhibition. Wells in which cells were treated with a saturating concentration (10 ng/ml) of a neutralizing anti- α 4 antibody (HP 2/1; Immunotech, Inc., Westbrook, ME) were used to determine the level of cell adhesion corresponding to 100% inhibition.

10 Cell adhesion in the presence of HP2/1 was usually less than 5% of that observed in the presence of vehicle alone. Percent inhibition was then calculated for each test well and the IC₅₀ was determined from an eight point titration using a validated four parameter fit algorithm.

15

EXAMPLE 16Antagonism of VLA-4 Dependent Binding to VCAM-Ig Fusion Protein.

20 Step A. Preparation of VCAM-Ig.
The signal peptide as well as domains 1 and 2 of human VCAM (GenBank Accession no. M30257) were amplified by PCR using the human VCAM cDNA (R & D Systems) as template and the following primer sequences: 3'-PCR primer: 5'-AATTATAATTGATCAACTTAC
25 CTGTCAATTCTTTACAGCCTGCC-3';
5'-PCR primer:
5'-ATAGGAATTCCAGCTGCCACCATGCCTGGGAAGATGGTCG-3'.
The 5'-PCR primer contained EcoRI and PvuII restriction sites followed by a Kozak consensus sequence (CCACC) proximal to the 30 initiator methionine ATG. The 3'-PCR primer contained a BclI site and a splice donor sequence. PCR was performed for 30 cycles using the following parameters: 1 min. at 94°⁰C, 2 min. at 55°⁰C, and 2 min. at 72°⁰C. The amplified region encoded the following sequence of human VCAM-1:
35 MPGKMWVILGASNILWIMFAASQAFKIEPPESRYLAQIGDSVSLTC
STTGCESPFPSWRTQIDSPLNGKVTNEGTTSTLMNPVSGNEHSYLC

TATCESRKLEKGIQVEIYSFPKDPEIHLGPLEAGKPIVKCSVADVY
PFDRLEIDLKGDHLMKSQEFLEDADRKSLETKSLEVTFTPVIEDIGK
VLVCRAKLHIDEMDSVPTVRQAVKEL. The resulting PCR product of
5 650 bp was digested with EcoRI and BclI and ligated to expression vector
pIg-Tail (R & D Systems, Minneapolis, MN) digested with EcoRI and
BamHI. The pIg-Tail vector contains the genomic fragment which
encodes the hinge region, CH2 and CH3 of human IgG1 (GenBank
Accession no. Z17370). The DNA sequence of the resulting VCAM
fragment was verified using Sequenase (US Biochemical, Cleveland,
10 OH). The fragment encoding the entire VCAM-Ig fusion was
subsequently excised from pIg-Tail with EcoRI and NotI and ligated to
pCI-neo (Promega, Madison, WI) digested with EcoRI and NotI. The
resulting vector, designated pCI-neo/VCAM-Ig was transfected into
CHO-K1 (ATCC CCL 61) cells using calcium-phosphate DNA
15 precipitation (Specialty Media, Lavalette, NJ). Stable VCAM-Ig
producing clones were selected according to standard protocols using
0.2-0.8 mg/ml active G418 (Gibco, Grand Island, NY), expanded, and cell
supernatants were screened for their ability to mediate Jurkat adhesion
to wells previously coated with 1.5 µg/ml (total protein) goat anti-human
20 IgG (Sigma, St. Louis, MO). A positive CHO-K1/VCAM-Ig clone was
subsequently adapted to CHO-SFM serum-free media (Gibco) and
maintained under selection for stable expression of VCAM-Ig. VCAM-
Ig was purified from crude culture supernatants by affinity
chromatography on Protein A/G Sepharose (Pierce, Rockford, IL)
25 according to the manufacturer's instructions and desalted into 50 mM
sodium phosphate buffer, pH 7.6, by ultrafiltration on a YM-30
membranes (Amicon, Beverly, MA).

Step B. Preparation of ¹²⁵I-VCAM-Ig

30 VCAM-Ig was labeled to a specific radioactivity greater than
1000 Ci/mmol with ¹²⁵I-Bolton Hunter reagent (New England Nuclear,
Boston, MA; cat # NEX120-0142) according to the manufacturer's
instructions. The labeled protein was separated from unincorporated
isotope by means of a calibrated HPLC gel filtration column (G2000SW;
35 7.5 x 600 mm; Tosoh, Japan) using uv and radiometric detection.

Step C. VCAM-Ig Binding Assay

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μ M. Jurkat cells were

5 centrifuged at 400xg for five minutes and resuspended in binding buffer (25 mM HEPES, 150 mM NaCl, 3 mM KCl, 2 mM glucose, 1 mM MnCl₂, 0.1% bovine serum albumin, pH 7.4) without MnCl₂. The cells were centrifuged again and resuspended in complete binding buffer.

Compounds were assayed in Millipore MHVB multiscreen plates (cat#

10 MHVBN4550, Millipore Corp., MA) by making the following additions to duplicate wells: (i) 200 μ L of binding buffer; (ii) 20 μ L of a working stock of ¹²⁵I-VCAM-Ig prepared in binding buffer (final assay concentration \pm 100 pM); (iii) 2.5 μ L of compound solution or vehicle alone; (iv) and 0.5 x 10⁶ cells in a volume of 30 mL. The plates were incubated at room

15 temperature for 30 minutes, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 μ L of binding buffer. After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat# 6005178), 100 μ L of microscint-20 (Packard cat# 6013621) was added to each well. The plates were then sealed, placed on

20 a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing vehicle alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition. Wells in which cells were treated with a saturating concentration of unlabeled VCAM-Ig (10 nM) were used to determine the

25 level of binding corresponding to 100% inhibition. Binding of ¹²⁵I-VCAM-Ig in the presence of 10 nM unlabeled VCAM-Ig was usually less than 5% of that observed in the presence of vehicle alone. Percent inhibition was then calculated for each test well and the IC₅₀ was

determined from a ten point titration using a validated four parameter fit algorithm. Compounds of Examples 1-8 showed IC₅₀ values of less

30 than 10 nM in the inhibition of VCAM-Ig binding to VLA-4. IC₅₀ values for the inhibition of VCAM-Ig binding to VLA-4 are provided below for representative compounds:

Antagonism of $\alpha_4\beta_1$ Dependent Binding to VCAM-Ig Fusion Protein.Step A. $\alpha_4\beta_1$ Cell line.

RPMI-8866 cells (a human B cell line $\alpha_4^+\beta_1^-\beta_7^+$; a gift from Prof. John Wilkins, University of Manitoba, Canada) were grown in RPMI/10% fetal calf serum/ 100 U penicillin, 100 μ g streptomycin/ 2 mM L-glutamine at 37°C, 5 % carbon dioxide. The cells (1.25×10^6 cells/well) were pelleted at 1000 rpm for 5 minutes and then washed twice in binding buffer (25 mM Hepes, 150 mM NaCl, 0.1 % BSA, 3 mM KCl, 2 mM Glucose, pH 7.4). Cells were then resuspended at 3.3×10^7 cells/ml.

Step B. VCAM-Ig Binding Assay

^{125}I -VCAM-Ig (prepared as above) was diluted in binding buffer to < 500 pM VCAM-Ig /10 μ l. (i.e. if specific activity VCAM-Ig = 3.5×10^6 cpm/pmole, then 250,000 cpm/well = 7.14×10^{-14} moles VCAM-Ig. The volume of the assay was 150 μ l, and the final concentration of VCAM-Ig = 476 pM). Compounds of the present invention and serial dilutions were prepared in DMSO. The final amount of DMSO in the assay was kept at 1% when adding 1.5 μ l diluted compound to each well.

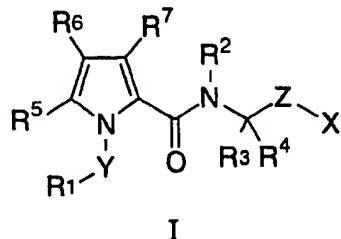
Compounds were assayed in Millipore MHVB multiscreen plates (Cat# MHVBN4550) by making the following sequential additions to duplicate wells: (i) 100 μ l/well of binding buffer containing 1.5 mM Mn⁺⁺; (ii) < 500 pM/well ^{125}I -VCAM-Ig; (iii) 1.5 μ l/well test compound; (iv) 38 μ l/well RPMI-8866 cell suspension (1.25×10^6 cells/well). Control wells were established as follows: (i) total binding = buffer + ^{125}I -VCAM-Ig + cells; (ii) non-specific binding = buffer + ^{125}I -VCAM-Ig - cells. Plates were incubated for 45 min. at 25°C on a plate shaker at 200 rpm. The multiscreen plates were filtered using a Millipore vacuum manifold (Cat. # MAVM 096 01). The plates were washed once with 100 μ l/well binding buffer + 1 mM Mn⁺⁺. After vacuum filtration, the plates were blotted, the plastic backing was removed and blotted again and allowed to air dry. When the filters were dry, the plates were transferred to Packard adapter plates (Cat# 6005178). Packard Microscint-20 (100 μ L/well) (Cat# 6013621) was added and the plates were sealed. The plates were placed on a plate shaker at 500 rpm for 30 seconds and counted on a Packard Topcount. Percent inhibition was then calculated

for each test well and the IC₅₀ was determined from a ten point titration using a validated four parameter fit algorithm.

WHAT IS CLAIMED IS:

1. A compound having the formula I:

5



or a pharmaceutically acceptable salt thereof wherein:

X is	1) -C(O)OR ^d ,
10	2) -P(O)(OR ^d)(OR ^e)
	3) -P(O)(R ^d)(OR ^e)
	4) -S(O) _m OR ^d ,
	5) -C(O)NR ^d R ^h , or
	6) -5-tetrazolyl;
15 Y is	1) -C(O)-,
	2) -O-C(O)-,
	3) -NR ^e -C(O)-,
	4) -S(O) ₂ -,
	5) -P(O)(OR ⁴) or
20	6) C(O)C(O);
Z is	1) a bond, or
	2) -C(R ⁸)(R ⁹)-;
R ¹ is	1) C ₁₋₁₀ alkyl,
	2) C ₂₋₁₀ alkenyl,
25	3) C ₂₋₁₀ alkynyl,
	4) Cy,
	5) Cy-C ₁₋₁₀ alkyl,
	6) Cy-C ₂₋₁₀ alkenyl,
	7) Cy-C ₂₋₁₀ alkynyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

5 R² is 1) hydrogen,
 2) C₁-10 alkyl,
 3) Cy,
 4) Cy-C₁-10 alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with
10 one to four substituents independently selected from R^b;

15 R³ is 1) hydrogen,
 2) C₁-10alkyl,
 3) C₂-10alkenyl,
 4) C₂-10alkynyl,
 5) Cy-(Cy)p,
 6) Cy-(Cy)p-C₁-10alkyl,
 7) Cy-(Cy)p -C₂-10alkenyl,
 8) Cy-(Cy)p -C₂-10alkynyl,

alkyl, alkenyl and alkynyl are optionally substituted with one to four
20 substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

25 R⁴ is 1) hydrogen,
 2) C₁-10alkyl,
 3) C₂-10alkenyl,
 4) C₂-10alkynyl,
 5) Cy,
 6) Cy-C₁-10alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^a, and Cy is optionally substituted with
30 one to four substituents independently selected from R^b;

30 R⁵, R⁶, and R⁷ are each independently

1) hydrogen, or
2) a group selected from R^b; or

R^5 and R^6 or R^6 and R^7 and the two adjacent carbon atoms to which they are attached, together form a 5-7 membered saturated or unsaturated monocyclic ring containing zero to two heteroatoms selected from N, O or S;

5 R^8 is 1) hydrogen,
 2) a group selected from R^a , or
 3) a group selected from R^1 ;

R^9 is 1) hydrogen,
 2) C_{1-10} alkyl,
 10 3) C_{2-10} alkenyl,
 4) C_{2-10} alkynyl,
 5) Cy,
 6) Cy- C_{1-10} alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to 15 four substituents selected from R^a , and Cy is optionally substituted with one to four substituents independently selected from R^b .

R^a is 1) $-CF_3$;
 2) $-OR^d$,
 3) $-NO_2$,
 20 4) halogen
 5) $-S(O)_mR^d$,
 6) $-SR^d$,
 7) $-S(O)_2OR^d$,
 8) $-S(O)_mNR^dR^e$,
 25 9) $-NR^dR^e$,
 10) $-O(CR^fR^g)_nNR^dR^e$,
 11) $-C(O)R^d$,
 12) $-CO_2R^d$,
 13) $-CO_2(CR^fR^g)_nCONR^dR^e$,
 30 14) $-OC(O)R^d$,
 15) $-CN$,
 16) $-C(O)NR^dR^e$,
 17) $-NR^dC(O)R^e$,
 18) $-OC(O)NR^dR^e$,

19) $-\text{NR}^d\text{C}(\text{O})\text{OR}^e$, or
20) $-\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{R}^e$;
21) $-\text{CR}^d(\text{N}-\text{OR}^e)$, or
22) Cy optionally substituted with a group independently selected from R^c ;

5 R^b is 1) a group selected from R^a ,
 2) C_{1-10} alkyl,
 3) C_{2-10} alkenyl,
 4) C_{2-10} alkynyl, or
10 5) Cy- C_{1-10} alkyl,
wherein alkyl, alkenyl, alkynyl, and Cy are optionally substituted with a group independently selected from R^c ;
substituted with a group independently selected from R^c ;

15 R^c is 1) halogen,
 2) amino,
 3) carboxy,
 4) C_{1-4} alkyl,
 5) C_{1-4} alkoxy,
 6) aryl,
20 7) aryl C_{1-4} alkyl, or
 8) aryloxy;

25 R^d and R^e are independently selected from the group consisting of
 1) hydrogen,
 2) C_{1-10} alkyl,
 3) C_{2-10} alkenyl,
 4) C_{2-10} alkynyl,
 5) Cy, and
 6) Cy C_{1-10} alkyl,
wherein alkyl, alkenyl, alkynyl and Cy is optionally substituted with one
30 to four substituents independently selected from R^c ; or
 R^d and R^e together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^f and R^g are independently selected from hydrogen, C₁-10alkyl, Cy and Cy C₁-10alkyl; or

5 R^f and R^g together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^h is

- 1) hydrogen,
- 2) C₁-10alkyl,
- 3) C₂-10alkenyl,
- 4) C₂-10alkynyl,
- 5) cyano,
- 6) aryl,
- 7) aryl C₁-10alkyl,
- 8) heteroaryl,
- 9) heteroaryl C₁-10alkyl, or
- 10) -SO₂Rⁱ;

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from R^b;

20 Rⁱ

- 1) C₁-10alkyl,
- 2) C₂-10alkenyl,
- 3) C₂-10alkynyl, or
- 4) aryl;

wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^c; Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl; m is an integer from 1 to 2; n is an integer from 1 to 10; and p is 0 or 1.

30

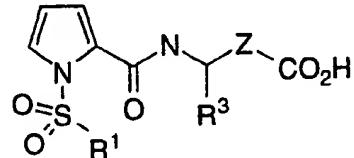
R¹ is

2. A compound of Claim 1 wherein
- 1) Cy, or
- 2) Cy-C₁-10alkyl

wherein alky is optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b.

5 3. A compound of Claim 1 wherein
Y is 1) -C(O)-, or
 2) SO₂.

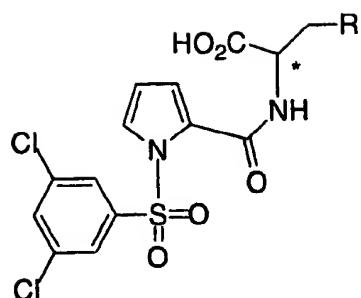
10 4. A compound of Claim 1 wherein X is -C(O)ORD.
 5. A compound of Claim 1 having the formula Ia:



Ia

15 wherein
R1 is aryl optionally substituted with one or two groups
independnetly selected from R^b;
R3 is 1) C₁₋₁₀alkyl,
 2) Cy-(Cy)_p, or
 3) Cy-(Cy)_p-C₁₋₁₀alkyl,
wherein alkyl is optionally substituted with one to four substituents
independnetly selected from R^a; and Cy is optionally substituted with
one to four substituents independently selected from R^b;
25 Z is 1) a bond, or
 2) -CH₂-.

6. A compound of Claim 1 selected from the group
consisting of:



wherein R is phenyl, benzyl, propyl, 4-(t-butoxyphenyl), 4-(benzyloxy)phenyl, 4-(2-methoxyphenyl)phenyl, 4-(3-methoxyphenyl)phenyl, 4-(2-cyanophenyl)phenyl, 4-(3-cyanophenyl)phenyl, 4-(2-propyloxyphenyl)phenyl, 4-(2-tetrazolylphenyl)phenyl, 4-(2-methylthiophenyl)phenyl, 4-(2-methylsulfonylphenyl)phenyl, or 4-hydroxyphenyl, and * represents that the stereoconfiguration is that of an L-amino acid.

10

7. A method for inhibiting cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

15

8. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

20

9. A method for the treatment of asthma in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

25

10. A method for the treatment of allergic rhinitis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

11. A method for the treatment of multiple sclerosis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

5 12. A method for the treatment of atherosclerosis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

10 13. A method for the treatment of inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

15 14. A method for the treatment of inflammatory bowel disease in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

15. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier thereof.

20 16. A method for inhibiting cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 2.

25 17. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 2.

30 18. A method for the treatment of asthma, allergic rhinitis, multiple sclerosis, atherosclerosis or inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 2.

19. A pharmaceutical composition which comprises a compound of Claim 2 and a pharmaceutically acceptable carrier thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24635

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 207/48
US CL :548/518, 537

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/518, 537

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARTICO et al. Synthesis of Pyrryl Aryl Sulfones. Arch. Pharm. December 1995, Vol. 328, No. 3, pages 223-229, especially page 225.	1-5, 19

Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	
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"E"	earlier document published on or after the international filing date
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"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
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"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"A"	document member of the same patent family

Date of the actual completion of the international search Date of mailing of the international search report

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